Remarks

This Reply is responsive to the Office Action mailed on September 27, 2005 and is accompanied by a petition for a one-month extension of time along with authorization to charge for the extension fee to charge account 50-0951. Claims 1-21 were pending at the time of the Office Action. Claims 22-33 were withdrawn from consideration pursuant to a telephone conversation between the Examiner and present counsel. Applicant herein confirms election of Group I, claims 1-21 and withdrawal of claims 22-33. Claims 1-21 were all rejected.

Specifically, claims 1, 3-4, 10-12, 16 and 20 were rejected under 35 U.S.C. §102(e) as being anticipated by Lefkowitz et al. (US 6,841,663). Claims 1-7, 10-12, 14-15 and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by Vo-Dinh (WO 00/43552; hereafter "Vo-Dinh WO"). Claims 1-7, 10-12, 14-15 and 20 were rejected under 35 U.S.C. §102(e) as being anticipated by Vo-Dinh (US 6,743,581; "hereafter "Vo-Dinh"). Claims 8-10 and 16-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vo-Dinh WO in view of Lipshutz et al. (US 5,856,174). Claim 13 was rejected under 35 U.S.C. §103(a) as being unpatentable over Vo-Dinh WO in view of Hammer et al. (US 6,391,264). Claim 21 was rejected under 35 U.S.C. §103(a) as being unpatentable over Vo-Dinh WO in view of Tanaami (US 6,458,545).

Claims 1-21 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27, 34, and 48 of copending Application No. 10/229,600. Claims 1-21 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 10/680,389. Claims 1-21 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Vo-Dinh.

Before reviewing the cited art, Applicant will first review the claimed invention as now recited in amended claim 1. Amended claim 1 recites (additions shown with an underline):

1. (Currently amended) An integrated circuit based multiplex sampling detection system, comprising:

a plurality of probe microarrays, each of said microarrays having a plurality of receptor probe elements each arranged as a 2-dimensional array of said probe elements, said probe elements for combining with at least one target molecule;

a source of electromagnetic radiation and associated optical devices for simultaneously irradiating said probes arranged on said 2-dimensional array, said probe elements generating an identifiable signal when combined with said target molecule in response to said electromagnetic radiation;

structure for translating said plurality of microarrays one by one into optical alignment with radiation from said source of radiation,

an integrated circuit microchip including a plurality of detection channels to which said probe elements are brought into optical alignment for simultaneously sensing the presence of said target molecule based on said identifiable signal across said 2-dimensional array, and

an electronic control system connected to said structure for translating for synchronizing operation of said system including time intervals for translating said plurality of microarrays, wherein after said optical alignment translation ceases while sensing takes place for a period time, wherein after said period of time said control system commands said structure for translating to align another of said microarrays into optical alignment with radiation from said source of radiation and said detection channels.

Support for the "2-dimensional array" of probe elements can be found in Figs. 2A, 2B, 3A and 3B, and the associated specification. Support for the claimed "source of electromagnetic radiation and associated optical devices for simultaneously irradiating said probes arranged on said 2-dimensional array" and "integrated circuit microchip including a plurality of detection channels for simultaneously sensing the presence of said target molecule across the 2-dimensional array" can be found in several places in Applicants' specification, including paragraph 63, 65 and 69 (copied below):

> [0063] A heating/cooling device (e.g. thermoelectronic Peltier chip) can provide thermal control of the reactions inside the sample delivery platform housing 222. The tape is aligned such that each set of microarray probes 212 is excited by light from light source 225, such as an LED or laser, after passing through optional bandpass filter 226 and being diffracted by diffracting optic/focussing lens 227. *Diffracting optic/focussing lens 227 can provide a plurality of excitation light beams, such as sixteen (16) to provide one light beam per probe, the respective light beams having an area to match the area of the respective receptor probes on microarray 212.* Reflective optic 229 directs the light beams produced by diffracting optic/focussing lens 227 towards microarray probes 216-219.
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> [0065] Biochip 240 includes integrated electrooptics, such as a photosensor microarray 242 based on an array of optoelectronic transducers, such as photodiodes, phototransistors or avalanche diodes. As shown in FIG. 2, the photosensor microarray includes sixteen (16) sensors, one for each receptor probe on microarray 212. This arrangement permits each detection channel to have customizable characteristics to match the associated bioreceptor, such as high gain for normally low signal levels. Although generally preferable to have one sensor for each receptor probe, the invention can clearly be practiced with an unequal number, such as possible through use of a multiplex switch.
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> [0069] The disk 310 is aligned such that each set of microarray probes 315 is excited by light from light source 325, such as a LED or laser, after passing through optional bandpass filter 326 and being diffracted by diffracting optic/focussing lens 327. Diffracting optic/focusing lens 327 can provide a plurality of excitation light beams, such as sixteen (16) to provide one light beam per probe 316-319, the respective light beams having an area to match the area of the respective receptor probes on microarray 315. Reflective optic 328 directs the light beams produced by diffracting optic/focussing lens 327 towards probes on microarray 315.

[0010] Support for the claimed "electronic control system connected to said structure for translating for synchronizing operation of said system including time intervals for translating said plurality of microarrays, wherein after said optical alignment translation ceases while sensing takes place for a period time, wherein after said period of time said control system commands said structure for translating to align another of said microarrays into optical alignment with radiation from said source of radiation and said detection channels" can be found in the last sentence of paragraph 40 together with Fig. 1 "An electronic control system 190 can be used to synchronize all system operations, including sample transport and translation of tape 165". Moreover paragraph 68 discloses:

> Figure 3A shows a biochip system 300 which includes a rotating disc 310 which provides a plurality of probe microarrays 315, each microarray 315 having a plurality of receptor probes 316-319. The disc 310 is mounted on a rotating platform (not shown) driven by a stepping motor 318, such that only a portion, such as one microarray, of disc 310 is rotated through the sample delivery platform 322 and exposed and aligned to the detection chip 340 at any given time. Once a detection cycle is performed, the disc 310 can be rotated so that successive portions of the disc 310 with a new set of microarray probes 316-319 are aligned above the integrated electrooptic chip 340.

Further support for the stop-and-go aspect of the claimed invention can be found in paragraph 28 which discloses " For example, a replenished microarray of receptor probes may be provided to replace a given probe microarray following passage of a predetermined period of time of operation or following an indication that the receptor sites currently in service are occupied to a predetermined extent". Moreover, paragraph 5 leading into paragraph 6 discloses "Translation of the microarrays permits a replenishable supply of probes to be provided, such as after a predetermined amount of time. The ability to provide a replenishable supply of probes permits continuous sampling and processing, other than the brief periods of time during microarray translation required to replace one microarray with another microarray".

[0011] Accordingly, Applicants claimed integrated circuit based detection system provides true multiplex sampling, where a plurality of probes in a 2-dimensional area are simultaneously radiated and sensed for the presence of target molecules. Movement of the probe arrays is driven by a translating structure which is controlled by an electronic control system. As noted above the claimed system aligns, exposes and senses the probes on one 2-D microarray at any given time. Once a detection cycle is performed, the a new set of microarray probes are aligned with the detector chip.

Turning now to the cited art, According to the Examiner regarding Lefkowitz:

> **Regarding Claim 1, Lefkowitz et al disclose an integrated circuit comprising a plurality of probe microarrays, each having a plurality of probe elements (Column 9, lines 4-55 and Fig. 1-2), a source of electromagnetic radiation (e.g. laser light source # 610, Column 20, lines 30-31 and Fig. 13) a structure for translating the plurality of microarrays wherein the microarrays are replaceable with the next microarray (i.e. motor connected to reel # 432, Column 61-67), and a circuit including a plurality of detection channels to which the probes are brought into alignment with (e.g. scanner, Column 19, lines 37-60).**

Applicant respectfully disagrees with several assertions regarding Lefkowitz noted above regarding the disclosed detection system. Lefkowitz is mainly concerned with methods, apparatus, and computer program products to form arrays of polymers, such as DNA, each having a pattern of features 16 on a surface of a flexible elongated "web" 10. Polymers or their precursor units are applied at an application station to the surface of the web. Multiple features are covered at a reagent station with a continuous volume of reagent which chemically reacts with precursors or the web. The flexible elongated web is driven in a lengthwise direction through the application station. This sequence may be repeated as needed to form the arrays along the web. Multiple arrays 12 can be disposed on web 10, and each array 12 can include multiple spots or features 16 of bioploymers.

Although the Examiner asserts that Lefkowitz discloses an integrated circuit, fluorescence detector 640 and light sensor 165 are not disclosed or suggested to be an integrated circuit-based sensors/detectors (chip). Moreover, although Lefkowitz discloses a fluorescence detector 640 to measure fluorescent light signals emanating from spots/features 16 on web 10, measurements are performed *one at a time*. The one at a time measurement scheme disclosed by Lefkowitz is made clear by col. 20, lines 30-37 of Lefkowitz (copied below) read in conjunction with Figs. 13 and 14:

> A light source such as a laser illuminates location 610 with beam 620, and any resulting fluorescence 630 from features 16 at detecting location 610, is detected at fluorescence detector 640. Detecting location 610 is moved back and forth across web 10 in the direction of axis 650 while web 10 is driven past detecting location in the direction 655, resulting in a scanned pattern illustrated at 635.

The web 10 is thus driven (moved) in direction 655 (say the "X" direction) while the detecting location (Probe spot) is moved in direction 650 (say the "Y" direction) which is orthogonal to direction 655 during the data collection. Scanned pattern 635 evidences that the movement is continuous and that only single feature is sensed at a given time. Thus, although the output reel 432 disclosed by Lefkowitz does disclose providing one microarray after another (the replaceable feature), in the vicinity of scanner 160, as noted above, 2-dimensional scanning is required to read individual spots/features in each microarray. The scanning and related single feature at a time aspect of Lefkowitz provides evidence that the fluorescence detector 640/ light sensor 165 is a non-pixelated, providing further evidence that the disclosed detector is a non-IC-based detector.

In contrast to Lefkowitz, Applicant's claimed detection system as amended includes "a source of electromagnetic radiation and associated optical devices for simultaneously irradiating said probes arranged on said 2-dimensional array" an "integrated circuit microchip including a plurality of detection channels to which said probe elements are brought into optical alignment for simultaneously sensing the presence of said target molecule based on said identifiable signal across said 2-dimensional array, and "an electronic control system" "for synchronizing operation of said system including time intervals for translating said plurality of microarrays". Accordingly, Applicant submits that amended claim 1 and its respective dependent claims are patentable over Lefkowitz. Although Applicant believes several of the dependent claims recite independently patentable features, in view of patentability of amended claim 1 discussion of such independently patentable features is moot and will not be presented for any of the cited references.

Claims 1-7, 10-12, 14-15 and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by Vo-Dinh (WO 00/43552). According to the Examiner:

> **Regarding Claim 1, Vo-Dinh discloses an integrated circuit comprising a plurality of probe microarrays, each having a plurality of probe elements (Fig. 8), a source of electromagnetic radiation (e.g. laser Fig. 6A), a structure for translating the plurality of microarrays wherein the microarrays are replaceable with the next microarray (i.e. translation stage, page 66, lines 10-27), and a circuit including a plurality of detection channels to which the probes are brought into alignment with (e.g. CCD, page 63-66 and Fig. 8).**

Unlike Lefkowitz, Vo Dinh WO does disclose a detection system including integrated circuit based detectors, such as based on phototransistors. However, like Lefkowitz, the disclosed system is capable of measuring only a single spot at a time and measurements are made as the spots are being moved relative to the detector. This deficiency is made clear by page 66, lines

10-34 (copied below; including "("As the DNA spot passed over the photodetector, a fluorescence signal is detected"):

> In this example the inventor developed and performed measurements using an amplifier-phototransistor (APT) device with 4.times.4 array of phototransistors. Whereas the CCD instrument was used to obtain an image of the microarray sample spots and to record a plot of the intensity, the signals from the APT microchip were directly recorded without the need of any electronic interface system or signal amplification device. The photocurrent of each sensing element of the APT microchip was transmitted directly into a digital photometer. The data from the photometer were linked to a personal computer (PC) via an RS-232 link. The samples consisted of an array of microspots of fluorescein-labeled DNA on a nitrocellulose membrane. In the study of the probe arrays on nitrocellulose membranes described in previous sections, the inventor used the CCD system to obtain a two-dimensional image of the fluorescence signals. Since the sensing elements of the phototransistor chip provide only signal intensity and not a signal profile, the inventor devised a device to record the response of the phototransistor detection elements as the sample spots were passed over the sensing elements. In this study, a nitrocellulose membrane having a series of fluorescein-labeled DNA sample spots was placed on a glass slide connected to a linear translation stage. *The measurements were made while the translation stage moved the sample arrays over the stationary phototransistor device.* Light from an argon ion laser at 488 nm was transmitted via an optical fiber and focused onto a sample spot. An appropriate optical filter placed between the sample substrate and the detector array was used to reject the laser radiation. *The data showed four resolved signals as the sample spots moved over an APT microchip channel. Four sample spots of 1-.mu.L of fluorescein-labeled DNA were placed on a nitrocellulose membrane, which was translated over a detection channel of an APT biochip. As the DNA spot passed over the photodetector, a fluorescence signal is detected.*

Accordingly, in contrast to Vo-Dinh WO, Applicant's claimed detection system as recited in amended claim 1 includes "a source of electromagnetic radiation *and associated optical devices for simultaneously irradiating said probes arranged on said 2-dimensional array*" an "integrated circuit microchip *for simultaneously sensing the presence of said target molecule based on said identifiable signal across said 2-dimensional array*", and "an electronic control system" "for synchronizing operation of said system including time intervals for translating said plurality of microarrays". Accordingly, Applicant submits that amended claim 1 and its respective dependent claims are patentable over Vo-Dinh WO.

Claims 1-7, 10-12, 14-15 and 20 were rejected under 35 U.S.C. §102(e) as being anticipated by Vo-Dinh (US 6,743,581). Regarding Vo-Dinh, the Examiner asserts:

Regarding Claim 1, Vo-Dinh discloses an integrated circuit comprising a plurality of probe microarrays, each having a plurality of probe elements (Fig. 8), a source of electromagnetic radiation (e.g. laser Fig. 6A), a structure for translating the plurality of microarrays wherein the microarrays are replaceable with the next microarray (i.e. translation stage, page 66, lines 10-27), and a circuit including a plurality of detection channels to which the probes are brought into alignment with (e.g. CCD, page 63-66 and Fig. 8).

Vo-Dinh is essentially the same disclosure as Vo-Dinh WO, and the Examiner's assertions above are identical as those made relative to Vo-Dinh WO. Therefore, Vo-Dinh does not disclose or suggest the claimed "a source of electromagnetic radiation *and associated optical devices for simultaneously irradiating said probes arranged on said 2-dimensional array*" an "integrated circuit microchip including a plurality of detection channels to which said probe elements are brought into optical alignment for simultaneously sensing the presence of said target molecule based on said identifiable signal across said 2-dimensional array, and "an electronic control system" "for synchronizing operation of said system including time intervals for translating said plurality of microarrays". Accordingly, in Applicant submits that amended claim 1 and its respective dependent claims are patentable over Vo-Dinh.

The amendments to claim 1 described above which add several unique features should remove the various double patenting rejections noted above.

Applicant has made every effort to present claims which distinguish over the cited art, and it is believed that all pending claims are in condition for allowance. However, Applicant requests the Examiner to call the undersigned (direct dial 561-671-3662) after review of this Reply if the Examiner determines that any clarification is necessary to permit issuance of a Notice of Allowance. If any fee other than the fees for one-month extension is due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,

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